A Control Theory for Stochastic Biomolecular Regulation

Corentin Briat, Ankit Gupta and Mustafa Khammash

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ETH
Eidgenössische Technische Hochschule Zürich
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CONTROL THEORY & SYSTEMS BIOLOGY

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Introduction

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Reaction networks

A reaction network is. . .

- A set of d distinct species $\boldsymbol{X_1}, \ldots, \boldsymbol{X_d}$
- A set of K reactions $R_1, \ldots, R_K$ specifying how species interact with each other and for each reaction we have
  - A stoichiometric vector $\zeta_k \in \mathbb{Z}^d$ describing how reactions change the state value
  - A propensity function $\lambda_k \in \mathbb{R}_{\geq 0}$ describing the "strength" of the reaction

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Deterministic networks

- Large populations (concentrations are well-defined), e.g. as in chemistry
- Lots of analytical tools, e.g. reaction network theory, dynamical systems theory, Lyapunov theory of stability, nonlinear control theory, etc.

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Stochastic networks

- Low populations (concentrations are NOT well defined)
- Biological processes where key molecules are in low copy number (mRNA $\simeq$10 copies per cell)
- No well-established theory for biology, “analysis" often based on simulations. . .
- No well-established control theory

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Chemical master equation

State and dynamics

- The state $X \in \mathbb{N}_0^d$ is vector of random variables representing molecules count
- The dynamics of the process is described by a jump Markov process $(X(t))_{t\geq 0}$

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Chemical Master Equation (Forward Kolmogorov equation)

$$\dot{p}_{x_0}(x,t) = \sum_{k=1}^{K} \lambda_k(x-\zeta_k)p_{x_0}(x-\zeta_k,t) - \lambda_k(x)p_{x_0}(x,t),\ x \in \mathbb{N}_0^d$$

where $p_{x_0}(x,t) = \mathbb{P}[X(t)=x|X(0)=x_0]$ and $p_{x_0}(x,0) = \delta_{x_0}(x)$.

Solving the CME

- Infinite countable number of linear time-invariant ODEs
- Exactly solvable only in very simple cases
- Some numerical schemes are available (FSP, QTT, etc) but limited by the curse of dimensionality; if $X \in \{0,\dots,\bar{x}-1\}^d$, then we have $\bar{x}^d$ states

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Ergodicity of reaction networks

Ergodicity

A given stochastic reaction network is ergodic if there is a probability distribution π such that for all $x_0 \in \mathbb{N}_0^d$, we have that $p_{x_0}(x,t) \to \pi$ as $t \to \infty$.

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Theorem (Condition for ergodicity[1])

Assume that

(a) *the state-space of the network is irreducible; and*

(b) *there exists a norm-like function $V(x)$ such that the **drift condition***

$$\sum_{i=1}^{K} \lambda_i(x)[V(x+\zeta_i) - V(x)] \leq c_1 - c_2 V(x)$$

holds for some $c_1, c_2 > 0$ and for all $x \in \mathbb{N}_0^d$. Then, the stochastic reaction network is ergodic.

[1] S. P. Meyn and R. L. Tweedie. Stability of Markovian processes III: Foster-Lyapunov criteria for continuous-time processes, *Adv. Appl. Prob.* , 1993

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holds for some $c_1, c_2 > 0$ and for all $x \in \mathbb{N}_0^d$. Then, the stochastic reaction network is ergodic.

Choosing $V(x) = \langle v, x \rangle$, $v > 0$, allows to establish the ergodicity of a wide class of existing reaction networks[2]

[1] S. P. Meyn and R. L. Tweedie. Stability of Markovian processes III: Foster-Lyapunov criteria for continuous-time processes, *Adv. Appl. Prob.* , 1993

[2] A. Gupta, C. Briat, and M. Khammash. A scalable computational framework for establishing long-term behavior of stochastic reaction networks, *PLOS Computational Biology*, 2014

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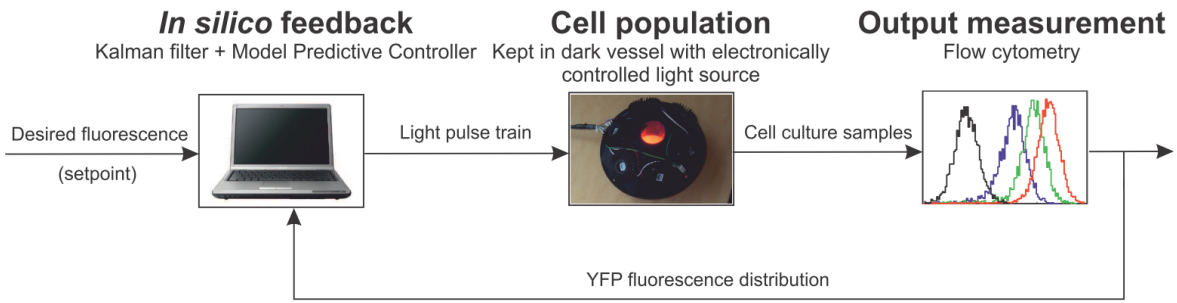
Control problems

In-silico control

- Controllers are implemented outside cells
- Single cell[1] or population control[2]



1 J. Uhlendorf, et al. Long-term model predictive control of gene expression at the population and single-cell levels, *Proceedings of the National Academy of Sciences of the United States of America*, 2012

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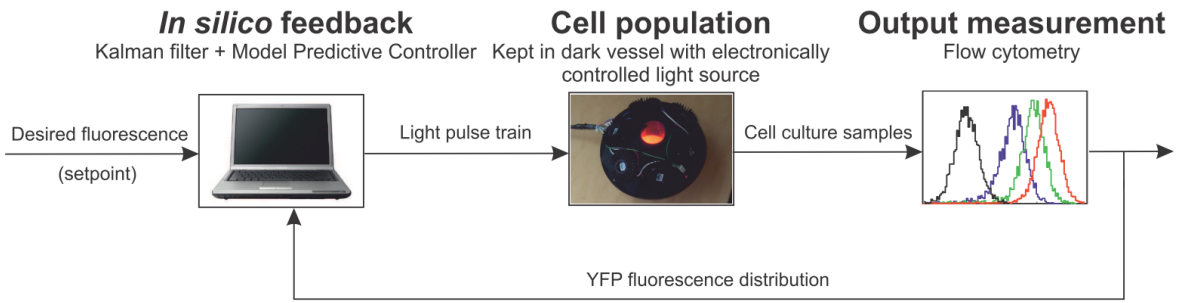
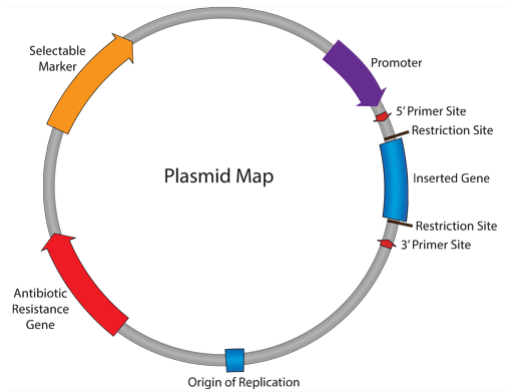


In-vivo control

- Controllers are implemented inside cells
- Single cell and population control[3]



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3 C. Briat, A. Gupta, and M. Khammash. Integral feedback generically achieves perfect adaptation in stochastic biochemical networks, *ArXiV*, 2015

In-vivo population control - Theory

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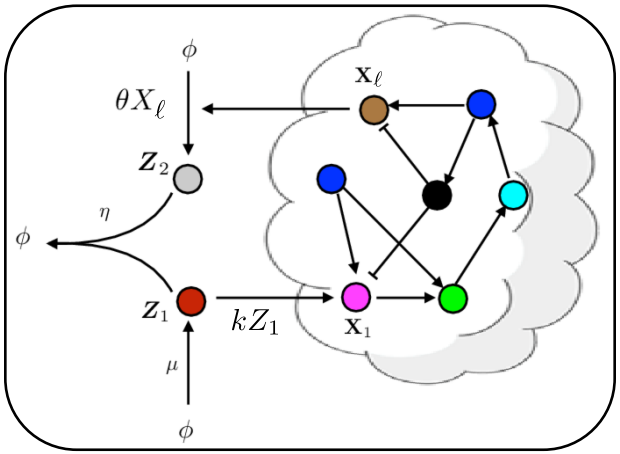
Setup

Open-loop reaction network

- d molecular species: $\boldsymbol{X_1, \ldots, X_d}$
- $\boldsymbol{X_1}$ is the actuated species: $\emptyset \xrightarrow{u} \boldsymbol{X_1}$
- Measured/controlled species: $\boldsymbol{Y = X_\ell}$



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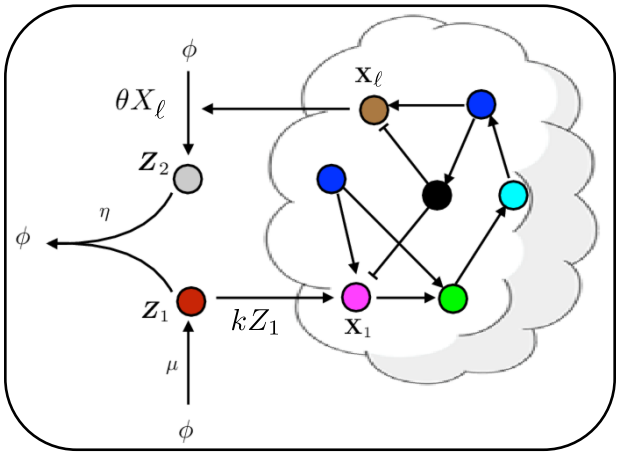

Problem

Find a controller such that the closed-loop network is ergodic and such that we have $\mathbb{E}[Y(t)] \to \mu$ as $t \to \infty$, for some reference value μ

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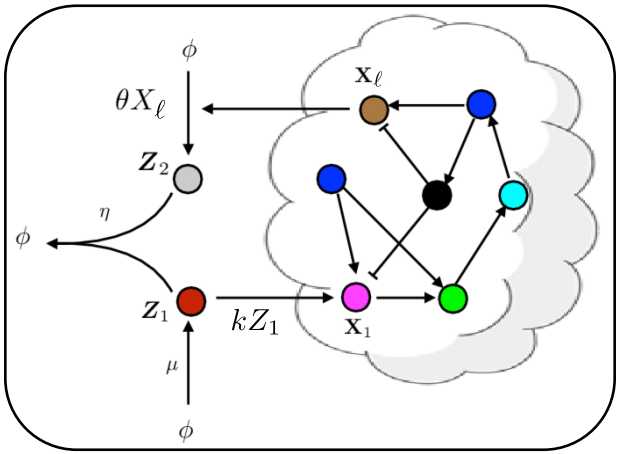

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The controller

- Two species $\boldsymbol{Z_1}$ and $\boldsymbol{Z_2}$.

$$\underbrace{\emptyset \xrightarrow{\mu} \boldsymbol{Z_1}}_{\text{reference}}, \quad \underbrace{\emptyset \xrightarrow{Y} \boldsymbol{Z_2}}_{\text{measurement}}, \quad \underbrace{\boldsymbol{Z_1 + Z_2} \xrightarrow{\eta} \emptyset}_{\text{comparison}}, \quad \underbrace{\emptyset \xrightarrow{kZ_1} \boldsymbol{X_1}}_{\text{actuation}}.$$

where $k, \eta > 0$ are control parameters.

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The hidden integral action[1]

Moments equations

$$\begin{aligned}\frac{d}{dt}\mathbb{E}[Z_1(t)] &= \mu - \eta\mathbb{E}[Z_1(t)Z_2(t)]\\ \frac{d}{dt}\mathbb{E}[Z_2(t)] &= \mathbb{E}[Y(t)] - \eta\mathbb{E}[Z_1(t)Z_2(t)].\end{aligned}$$

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Integral action

- We have that
$$\frac{d}{dt}\mathbb{E}[Z_1(t) - Z_2(t)] = \mu - \mathbb{E}[Y(t)],$$
so we have an integral action on the mean
- Closed-loop ergodic $\Rightarrow \mathbb{E}[Y(t)] \to \mu$ as $t \to \infty$
- No need for solving moments equations $\to$ no closure problem :)

[1] K. Oishi and E. Klavins. Biomolecular implementation of linear I/O systems, *IET Systems Biology*, 2010

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General stabilization result

Theorem

Let $V(x) = \langle v, x \rangle$ with $v \in \mathbb{R}^d_{>0}$ and $W(x) = \langle w, x \rangle$ with $w \in \mathbb{R}^d_{\geq 0}$, $w_1, w_\ell > 0$. Assume that

(a) *the state-space of the open-loop reaction network is irreducible; and*

(b) *there exist $c_1, c_3 > 0$ and $c_2 \geq 0$ such that*

$$\begin{aligned} \sum_{k=1}^{K} \lambda_k(x)[V(x+\zeta_k) - V(x)] &\leq -c_1 V(x), \\ \sum_{k=1}^{K} \lambda_k(x)[W(x+\zeta_k) - W(x)] &\geq -c_2 - c_3 x_\ell, \end{aligned} \tag{1}$$

hold for all $x \in \mathbb{N}^d_0$ (together with some other technical conditions).

Then, the closed-loop network is ergodic and we have that $\mathbb{E}[Y(t)] \to \mu$ as $t \to \infty$.

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Unimolecular networks

Theorem

Let us consider a unimolecular reaction network with irreducible state-space. Assume that its first-order moments system

$$\begin{aligned} \frac{d}{dt}\mathbb{E}[X(t)] &= A\mathbb{E}[X(t)] + e_1 u(t) \\ y(t) &= e_\ell^T \mathbb{E}[X(t)] \end{aligned} \tag{2}$$

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is

(a) *asymptotically stable, i.e* A *Hurwitz stable (LP)*

(b) *output controllable, i.e.* $\operatorname{rank}\begin{bmatrix} e_\ell^T e_1 & e_\ell^T A e_1 & \dots e_\ell^T A^{d-1} e_1 \end{bmatrix} = 1$ *(LP)*

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Then, for all control parameters $k, \eta > 0$*,*

(a) *the closed-loop reaction network (system + controller) is ergodic*

(b) *all the first and second order moments of the random variables* $X_1, \dots, X_d$ *are uniformly bounded and globally converging*

(c) $\mathbb{E}[Y(t)] \to \mu$ *as* $t \to \infty$*.*

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Properties

Closed-loop system

- Robust ergodicity, tracking and disturbance rejection
- Population control is achieved

Controller

- Innocuous: open-loop ergodic & output controllable $\Rightarrow$ closed-loop ergodic
- Decentralized: use only local information (single-cell control)
- Implementable: small number of reactions

Additional remarks

- No moment closure problem
- Expected to work on a wide class of networks (even though the theory is not there yet)

In-vivo population control - Example

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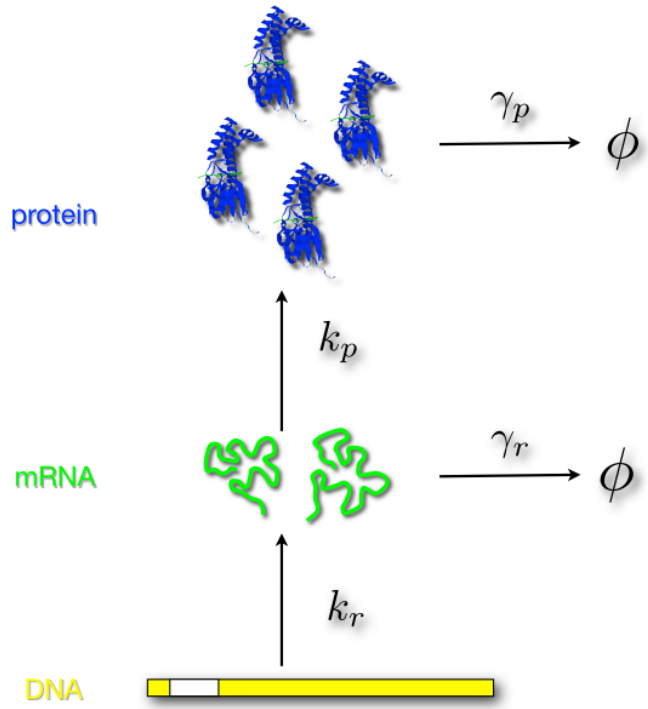
Gene expression network $d = 2$, $K = 4$



$$
\begin{aligned}
R_1 &: \emptyset \xrightarrow{k_r} \text{mRNA } (\boldsymbol{X_1}) \\
R_2 &: \text{mRNA} \xrightarrow{\gamma_r} \emptyset \\
R_3 &: \text{mRNA} \xrightarrow{k_p} \text{mRNA+protein } (\boldsymbol{X_1} + \boldsymbol{X_2}) \\
R_4 &: \text{protein} \xrightarrow{\gamma_p} \emptyset
\end{aligned}
$$

$$
\begin{aligned}
S &= \begin{bmatrix} \zeta_1 & \zeta_2 & \zeta_3 & \zeta_4 \end{bmatrix} \\
&= \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}
\end{aligned}
\qquad
\begin{aligned}
\lambda(x) &= \begin{bmatrix} \lambda_1(x) & \lambda_2(x) & \lambda_3(x) & \lambda_4(x) \end{bmatrix}^T \\
&= \begin{bmatrix} k_r & \gamma_r x_1 & k_p x_1 & \gamma_p x_2 \end{bmatrix}^T
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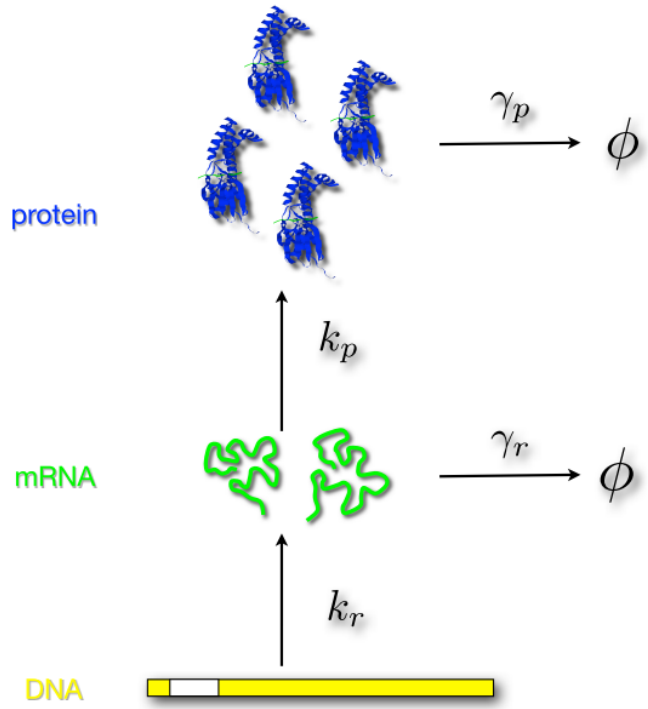

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$$

We want to control the average number of proteins by suitably acting on the transcription rate k_r

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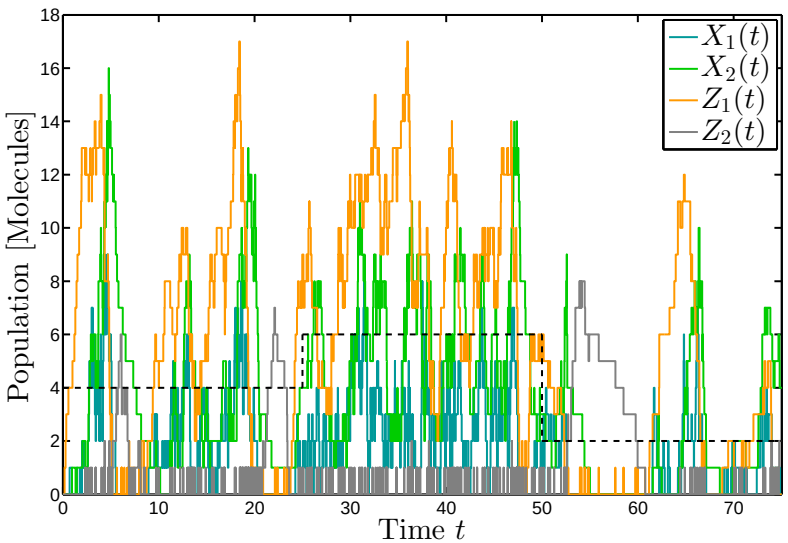
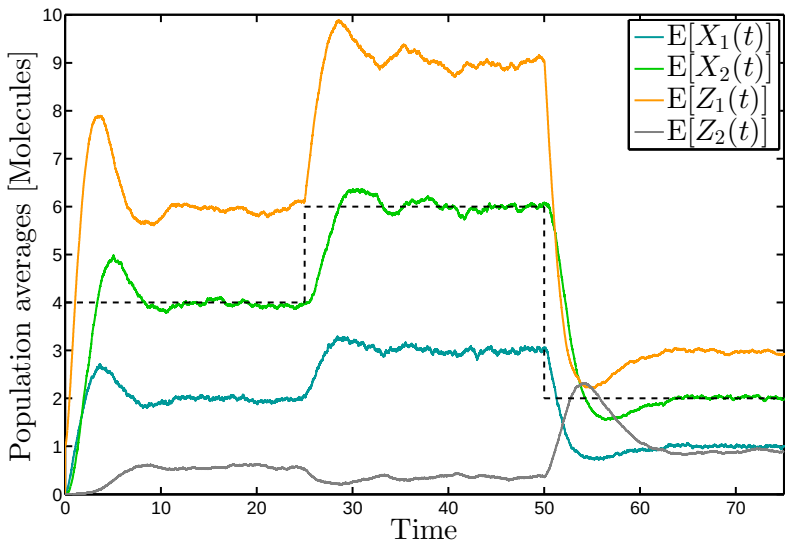
Gene expression control

Theorem

For any values of the system parameters $k_p, \gamma_r, \gamma_p > 0$ and the control parameters $\mu, k, \eta > 0$, the closed-loop network is ergodic and we have that $\mathbb{E}[X_2(t)] \to \mu$ as $t \to \infty$ globally.





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Comparison with deterministic control

Deterministic

$$
\begin{aligned}
\dot{x}_1 &= k z_1 - \gamma_r x_1 \\
\dot{x}_2 &= k_p x_1 - \gamma_p x_2 \\
\dot{z}_1 &= \mu - \eta z_1 z_2 \\
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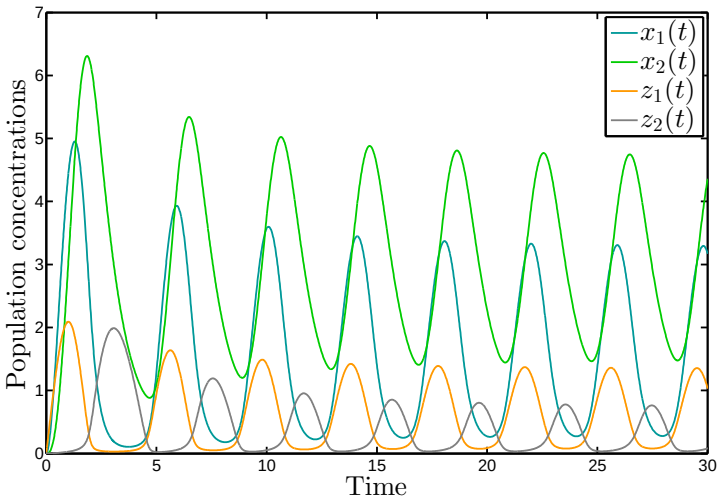

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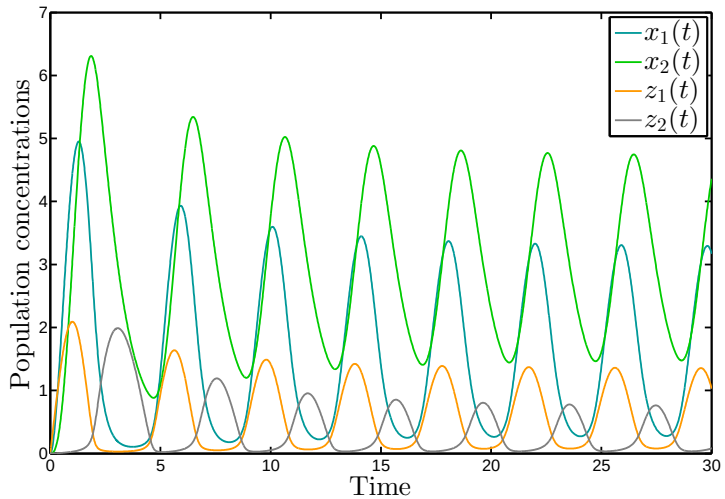

Stochastic

$$
\begin{aligned}
\dot{\mathbb{E}}[X_1] &= k\mathbb{E}[Z_1] - \gamma_r \mathbb{E}[X_1] \\
\dot{\mathbb{E}}[X_2] &= k_p \mathbb{E}[X_1] - \gamma_p \mathbb{E}[X_2] \\
\dot{\mathbb{E}}[Z_1] &= \mu - \eta \mathbb{E}[Z_1]\mathbb{E}[Z_2] \\
&\quad -\eta V(Z_1, Z_2) \\
\dot{\mathbb{E}}[Z_2] &= \mathbb{E}[X_2] - \eta \mathbb{E}[Z_1]\mathbb{E}[Z_2] \\
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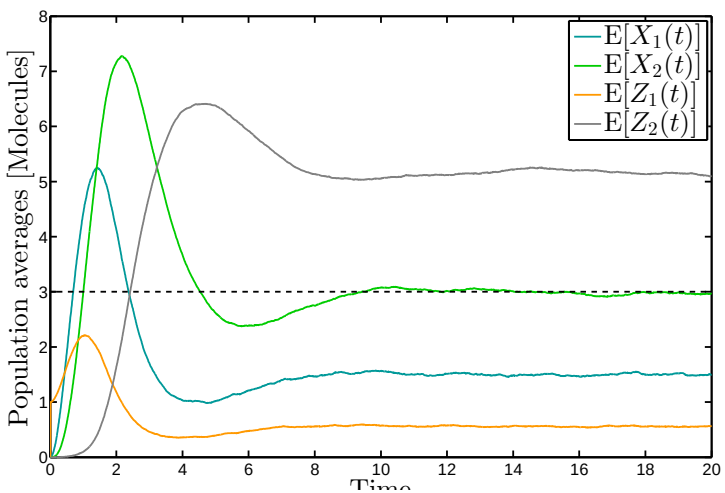

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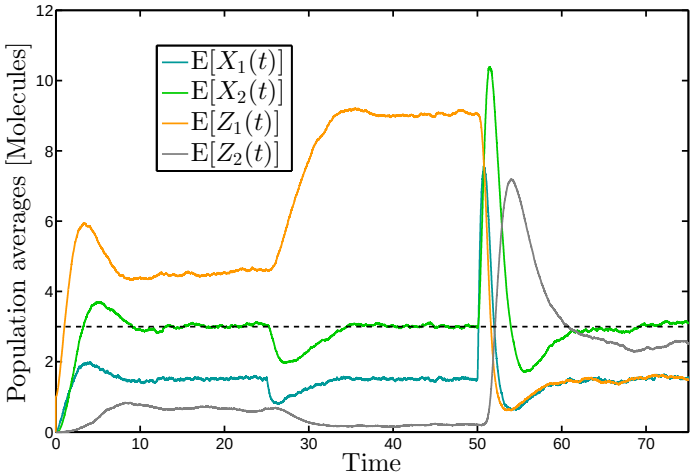
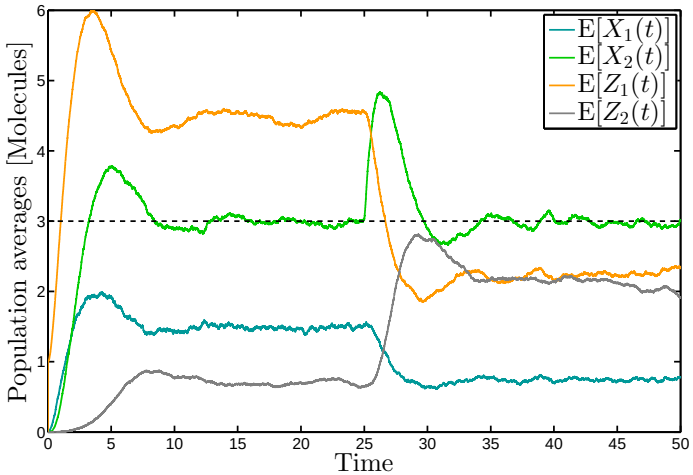
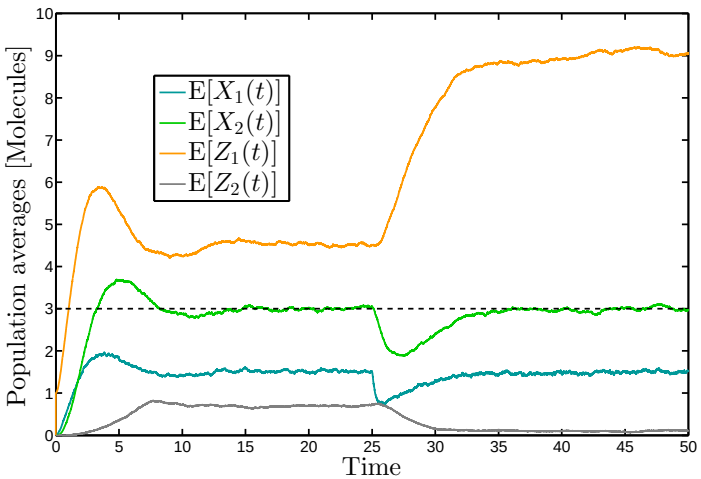
Robustness - Perfect adaptation



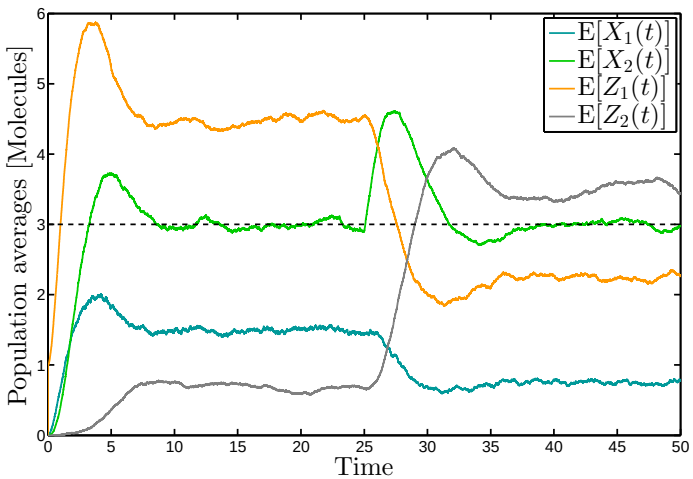
(a) Perturbation of the controller gain k



(b) Perturbation of the translation rate k_p



(c) Perturbation of the mRNA degradation rate



(d) Perturbation of the protein degradation rate

Concluding statements

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Concluding statements

What has been done

- In-vivo (integral) control motif seems promising
- Population control
- Perfect adaptation

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Concluding statements

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What has been done

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What needs to be done

- Implementation
- Extensions: bimolecular networks, different inputs, multiple inputs/outputs, different control motifs $\rightarrow$ biomolecular control theory

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Thank you for your attention

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Computational results

Theorem

The following statements are equivalent:

(a) *The matrix* A *is Hurwitz and the triplet* (A, e_1, e_ℓ^T) *is output-controllable.*

(b) *There exist* $v \in \mathbb{R}^d_{>0}$ *and* $w \in \mathbb{R}^d_{\geq 0}$ *with* $w^T e_1 > 0$, $w^T e_\ell > 0$, *such that*

$$v^T A < 0 \quad \text{and} \quad w^T A + e_\ell^T = 0.$$

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Comments

- Linear program
- Can be robustified $\rightarrow$ if $A \in [A^-, A^+]$, then $v_+^T A^+ < 0$ and $w_-^T A^- + e_\ell^T = 0$.
- Can be made structural $\rightarrow$ $A \in \{\ominus, 0, \oplus\}^{d \times d}$

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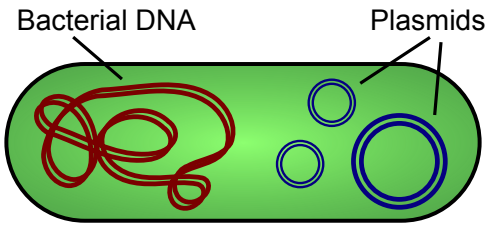
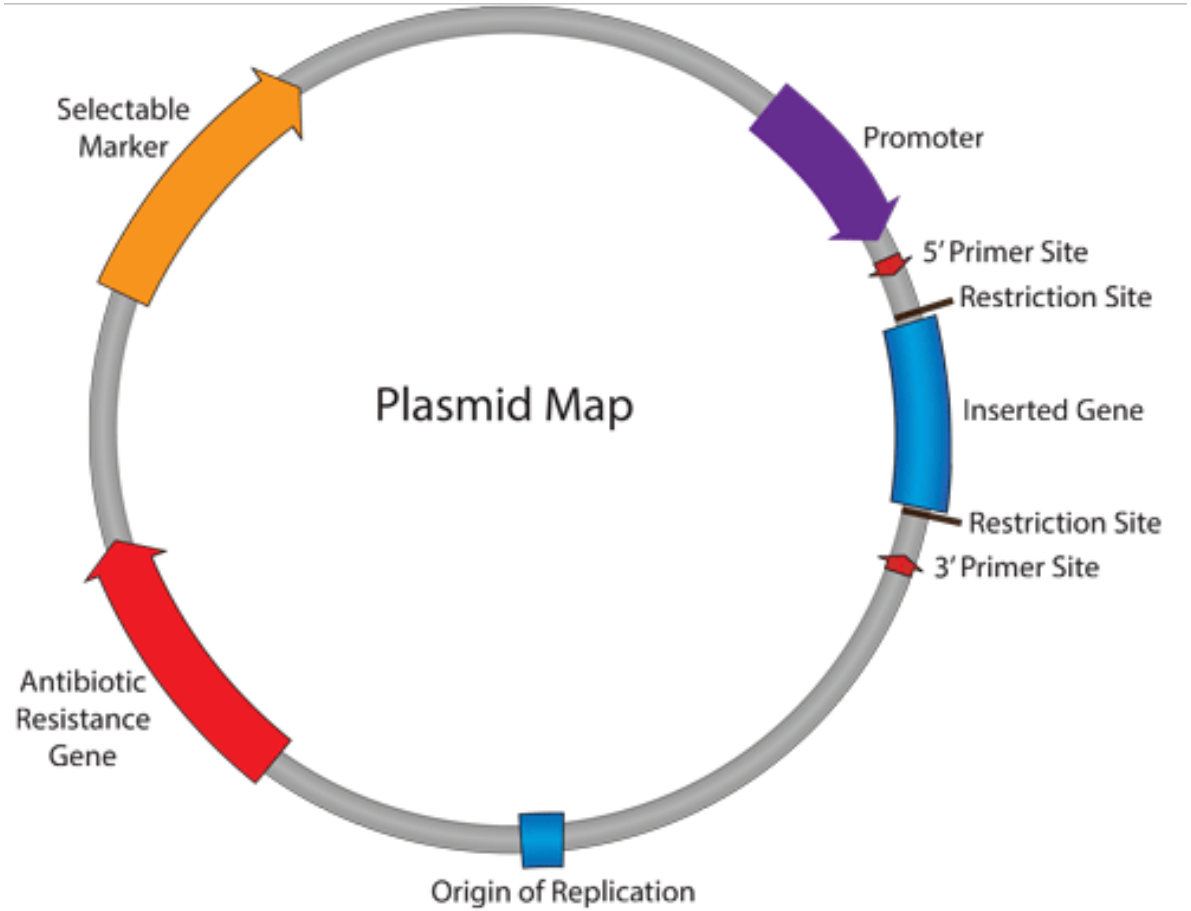
Implementation





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